REMARKS

Claims 39, 43, 44, 46-49, 51-53 are active in the subject application. Undersigned counsel thanks Examiner Crane for the interview on January 20, 2004, the main points are summarized below.

The claims have been clarified by reciting three specific 5'-phosphates. Support is at page 13, lines 17-20 ("uridine phosphates"), which a person of skill in the art would understand refers to 5'-mono, di- and tri-phosphates, as shown in the first Wurtman Declaration (concerning the biosynthesis of uridine phosphates) and paragraph 3 of the second Wurtman Declaration, submitted herewith.

Rejections under 35 U.S.C. 112, first paragraph

Claims 39, 43, 44, and 46-49 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification is such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner has pointed out that the instant disclosure reveals no specific test data to support the generic limitation "enhancing memory" and therefore, lacks any enabling effect. Applicants respectfully traverse this rejection.

A key finding in the instant application is embodied in FIG. 4, which shows that the oral administration of uridine causes enhancement of both cytidine and uridine concentrations within brain tissue. The results in FIG. 4 surprisingly indicate that uridine alone, once transported into the brain, is converted into cytidine in significant amounts. At the time these experiments were

being done, it was not apparent to those of ordinary skill in the art that brain uridine is converted into cytidine. Indeed, no such enzyme had been identified, and yet the results demonstrated an increase in brain cytidine following the sole administration of uridine. Where brain cytidine levels had been experimentally or therapeutically elevated in the past, uridine had been used in conjunction with other compounds (e.g., cytidine itself) that could have accounted for the observed rise in cytidine (Monticone GF, Minerva Med, 1966 Dec. 19; 57(101): p4348); or, uridine was not used at all (e.g., CDP-choline; Spiers PA, Arch Neurol, 1996; (53) p441). Second Wurtman Declaration, paragraphs 3-6.

What was apparent at the time the invention was made, however, was that a 39% rise in brain cytidine levels had clear implications for enhancing memory. It was known that both brain cytidine and brain uridine are eventually converted into cytidine triphosphate ("CTP"), which controls the rate of neuron membrane synthesis (discussed below). Importantly, raising the brain CTP level was known to increase neuron membrane synthesis because the CTP level controls the rate at which brain neurons produce phosphatides, such as phosphatidylcholine ("PC") and phosphatidylethanolamine ("PE"), which are the major constituents of brain membranes. Hence, a treatment that increased CTP levels would tend to increase the formation of brain membranes like the synaptic membranes responsible for communications between neurons. Second Wurtman Declaration, paragraph 9.

Therefore, with regard to enablement of the present method for enhancing memory, a person of ordinary skill in the art would have understood, when the invention was made, that enhancing brain cytidine levels in general should improve memory, and that a 39% increase in brain cytidine would likely be sufficient for that purpose. In fact, having knowledge of the data

of FIG. 4, an artisan would have had enough information to use uridine for "enhancing memory." For example, Applicants had previously shown that when aging human subjects were given a cytidine source (i.e., CDP-choline), some of their memory deficits were ameliorated (Spiers PA, Arch Neurol, 1996; (53) p441). Moreover, the experiments presented in the first Wurtman Declaration could have been conducted with no additional information other than that provided by FIG. 4 and what was known to one of ordinary skill in the art when the invention was made.

For at least these reasons, Applicants respectfully submit that all the pending claims are enabled by the specification and claims as filed. Accordingly withdrawal of the 112 rejections of claims 39, 43, 44, and 46 – 49, and their allowance is hereby solicited.

Rejections under 35 U.S.C. 112, second paragraph

Claims 39, 43, and 44 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner disputes the Applicants' position that the terms "uridine phosphate" and "a uridine phosphate" mean only 5'-UMP, 5-UDP, and/or 5'-UTP in the context of the present specification.

While Applicants respectfully disagree for the reasons previously filed with the first Wurtman Declaration, in the interest of speeding prosecution, claims 39, 43, and 44 have been amended to recite "a uridine phosphate selected from the group consisting of uridine 5'-monophosphate, uridine 5'-diphosphate and uridine 5'-triphosphate." The 35 U.S.C. 112, second paragraph, rejections are hereby believed to be rendered moot, and the Applicants respectfully request the allows of claims 39, 43, and 44.

Rejections under 35 U.S.C. § 102(b)

Claims 39, 43, and 44 stand rejected under under 35 U.S.C. § 102 as being anticipated by Ruthrich et al. ("Ruthrich"). Examiner notes that the abstract of the reference teaches that the administration of uridine is correlated with enhanced memory retention in rats.

A rejection under 102 is only proper when the claimed subject matter is identically described or disclosed in the prior art. M.P.E.P. 706.02(a). As amended, the present invention is directed to "*orally* administering" uridine phosphates. In contrast, the teachings of Ruthrich relate to the intraventricular injection of uridine dissolved in cerebrospinal fluid. Accordingly, because Ruthrich does not identically disclose the subject matter of the rejected claims, Applicants respectfully request that this rejection be withdrawn.

Claims 39, 43, and 44 also stand rejected under under 35 U.S.C. § 102 as being anticipated by Miyazaki et al. ("Miyazaki"). This document was published 27 November 1998, which was after the priority date of this application (31 July 1998; provisional application 60/095,002). Accordingly, Miyazaki is not prior art.

Rejections under 35 U.S.C. 103(a)

Claims 39, 43, and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Piazza et al, US Patent No. 5,962,459 ("Piazza"). Piazza teaches using uridine to counteract neuronal degeneration by stimulating cell growth. The Examiner adds that Applicants argued that treatment with uridine is entirely equivalent to treatment with a 5'-uridine phosphate. Applicants respectfully traverse this rejection.

The claims of the present invention are directed to enhancing memory by the oral administration of a uridine phosphate. Without being held to theory, as evidenced by the 132 Declaration submitted herewith, uridine and cytidine are both thought to enhance memory by facilitating production of synaptic membranes in a mammal, and brain levels of both compounds are raised in the claimed method.

Piazza teaches the use of uridine as a growth promoter (e.g. cell proliferation) and recites that "uridine is capable not only or reverting [*sic*, of reversing] the harmful effects induced in cell cultures . . . but, and this is by far more important, that it can act as a growth promoter" (see column 3, line 31). Piazza relates to a cell growth promoter and further recites "we discovered that uridine can give the same results of [*sic*, as] NGF when the growth factor is withdrawn from the medium" (see column 3, line 39). Accordingly, Pizza discloses the use of uridine *in cell cultures* to promote cell proliferation.

No experiments were conducted in animal models and no test results are shown for the treatment of neurological disorders or enhancing memory in a mammal. In other words, Piazza merely discloses the use of uridine as a means of promoting cell proliferation *in vitro*. Accordingly, Pizza does not disclose a method of enhancing memory by increasing cytidine levels. In fact, Pizza is completely silent on memory, on increasing cytidine levels, and on the effect of uridine administration on cytidine levels. For at least these reasons, Applicants respectfully request that this rejection be withdrawn.

Claims 39, 43, and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Polifarma, EPO Application No. 0178267 ("Polifarma"). Applicants respectfully traverse this rejection.

In order for a § 103 rejection to be proper, the combination of references must teach or suggest all limitations of the claim limitations. M.P.E.P. 2143.

The present claims are directed to "orally administering" uridine phosphates. In contrast, the teachings of Polifarma relate to the venal injection of uridine (Page 5, line 4). Accordingly, because Polifarma does not identically disclose the subject matter of the rejected claims, Applicants submit that a §103 rejection is improper and respectfully request that this rejection be withdrawn.

Claims 39, 43, and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Merlini et al., PTO-892 ref "T," ("Merlini"). Examiner notes that the abstract teaches the administration of uridine is effective in improving several mental functions including memorization. Applicants respectfully traverse this rejection.

The Merlini reference discloses the use of large doses of cytidine *combined with* uridine, and, in addition, it does not teach the use of a uridine-phosphate, as in the claimed invention. Therefore, Merlini does not teach or suggest a method of increasing brain cytidine levels according to the claimed invention, nor does it provide a motivation to combine to do so.

Accordingly, because Merlini does not identically disclose the subject matter of the rejected claims, Applicants submit that a §103 rejection is improper and respectfully request that this rejection be withdrawn.

Interview Summary

At the interview, Examiner Crane questioned how well gerbil test subjects represent human cases, and whether there was a corresponding sensitivity to UMP administration in

gerbils and humans. (Applicants note that in the Interview Summary, second paragraph, "mice" should read "gerbils". Also, in the second paragraph, the UA reference teaches UMP administration "intraventriculary," and not "intracranially.") It is noted that at page 12, lines 7 – 10 of the specification, gerbils were specifically selected over other possible laboratory rodents (e.g., mice, rats) because gerbils are believed to have pyrimidine metabolism that is most representative of humans. Furthermore, gerbils are accepted in the art as being most suitable for modeling brain disorders. ("For practical and ethical reasons humans cannot always be used for certain experimental experimental studies and those skilled in the art generally recognize that the gerbil model is equivalent to a human model. Indeed, gerbil models are the choice model for certain human diseases and brain disorders such as cerebral ischemia.") Ginsburg, et al., *Stroke* 20:1627-42, 1989.

CONCLUSION

In view of the forgoing remarks and data in the second Wurtman Declaration under 37 CFR 1.132, the claims are now in condition for allowance. Early notification of such action is solicited.

If the Examiner believes there is any issue which could be resolved by a telephone or personal interview, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Docket No.: 215055.0701
Customer No. 27160

PATENT
Serial No. 09/363,748

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this Response, or credit any overpayment to Deposit Account No. 50-0436.

In the event that an extension of time is required, or may be required in addition to that requested in a petition for an extension of time, the Commissioner is hereby requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-1710.

Respectfully submitted,

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